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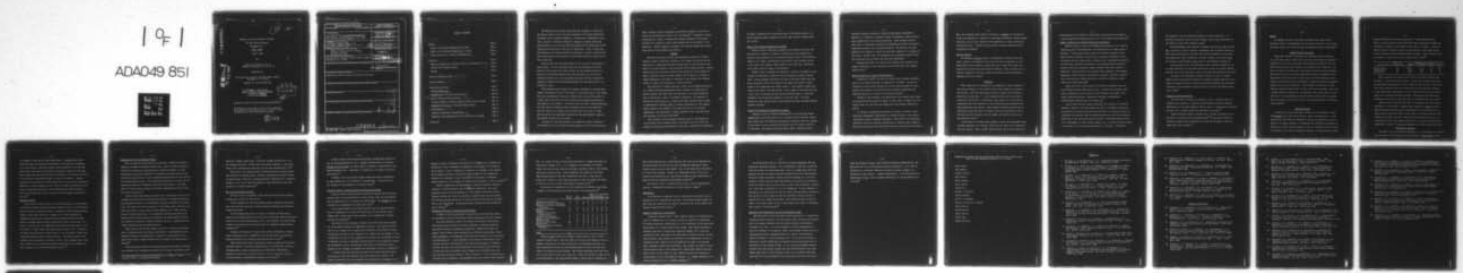

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Vehicles for the Application of Drugs for Oral Mucosal Disease

December 1973

FINAL REPORT

1964 - 1968

By

Austin H. Kutscher, D. D. S.
Edward V. Zegarelli, D. D.S., M. S.

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For many years it has been appreciated that attempts to treat acute and chronic lesions of the oral mucous membranes with topical medications (including chronic marginal gingivitis, the keratoses, desquamative stomatitis, recurrent ulcerative stomatitis, pemphigus, erythema multiforme, drug eruptions, etc.) have been severely hampered by the difficulty in maintaining such medications at the site of application. About 14 years ago, investigations were initiated aimed at developing a carrier or vehicle into which drugs might be incorporated and which might overcome at least some of these obstacles.[1]

Certain qualities were deemed essential for the use of any vehicle in human beings: (1) the components should not be irritating to the oral mucosal surfaces which they would contact; (2) the vehicle should be innocuous in the gastrointestinal tract when swallowed; (3) it should be relatively pleasant as to both sensation and taste; and (4) it should be compatible (physically and pharmacologically) with any drugs which it was intended to carry.

Since numerous mouth lesions are, indeed, moderately or severely symptomatic, particularly those of the erosive or ulcerative type, it was deemed even more advantageous to develop a vehicle which not only would serve as a drug carrier but which would also function as an adherent-protectant of the surfaces of the lesions. It was felt that were such a vehicle developed, not only would its adherence afford continued contact of the medication with the region to be treated, but, of great importance also, it would coat and protect the symptomatic lesions from the many chemical, physical and thermal irritations in the mouth.

In order to critically evaluate a new vehicle's carrier potential or its adhesive-protectant function following application to oral mucosal sur-

faces, numerous clinical techniques, specifically designed to test the validity and reliability of results, had to be devised.[2] A discussion of these investigations, however, is beyond the intended parameters of this paper and hence are referred to only in the references at the conclusion of the manuscript. Rather, emphasis is placed on the clinical studies and formulations which evolved through these efforts.

Orabase

The first formulation studied, and subsequently marketed as Orabase, offered a number of desirable properties as an adhesive protectant vehicle, especially for maintaining topically applied drugs on the oral mucous membranes for longer periods of time than heretofore had been possible. Initial studies with this formulation indicated that 60-250 mg of this vehicle adhered to applied sites for periods varying from 15 minutes to 2 hours or longer,[3] depending on the degree of mobility of oral tissues, the "washing action" of saliva, and the amount of vehicle applied.[1]

The components of Orabase (gelatin, pectin, and carboxymethylcellulose in a liquid petrolatum-polyethylene base), selected in a relatively empirical fashion, have been found over the years to be nearly completely free of deleterious, toxic, or allergenic properties. No evidences of irritation, side-reactions, or toxicity have been observed either locally or systemically following single or repeated applications of the adhesive vehicle except in one patient. The latter was found to be allergic, responding to the application of minute quantities with a discrete giant hive reaction on the back of the neck.[1]

The advantages over previously available vehicles were defined as: (1) increased contact-duration time of the tissues with the active component; (2) increased effectiveness of the active components by maintenance

of higher concentrations at the desired site; (3) decreased amount of an active drug which need be applied at any one time; and (4) a marked protective action.[1]

Study of the Adhesive Properties of Orabase

Various clinical tests[3] were undertaken which indicated that the average duration of adhesion of Orabase to various oral sites ranged from: anterior labial gingivae, 24-109 minutes; mucobuccal fold, 108-152 minutes; dorsum of the tongue, 25-58 minutes; hard palate, 23-281 minutes; mucosae of the cheek, 25-91 minutes; inner surface of the lower lip, 103 minutes; lower lingual anterior region, 34-85 minutes.[1]

Another study to determine the duration of adhesion of Orabase to oral tissues in "oriented" or "trained" subjects indicated a greater duration time: anterior gingivae and mucobuccal fold in the upper cuspid area, 2¾ hours; mucobuccal fold in the region of the lower first molar, 2 hours; dorsum of the tongue near the lateral border, 1 hour; anterior region (midline) of the vault of the hard palate, 1 hour; center of the buccal mucosae, 1 hour; floor of the mouth in the incisor (midline) region, 1 hour; and, mucobuccal fold and mucosae (midline) of the lower lip, 1 3/4 hours. Studies in clinic patients also fully confirmed the above prolonged adhesive duration findings.[1]

Study of the Protectant Properties of Orabase

During the course of these investigations[4] it was noted that Orabase demonstrated a protectant action, i.e., certain erosive ulcerative lesions when coated with this "inactive" preparation, appeared to heal more rapidly as the result of being covered and protected from the constant irritants in the mouth. Such lesions included, among others: traumatic ulcers,

recurrent ulcerative stomatitis, erosive lichen planus, desquamative gingivitis or stomatitis, idiopathic chronic inflammation, chronic discoid lupus erythematosus, and erythema multiforme. These patients reported some relief of symptomatic discomfort ("diminished pain and/or discomfort," "decreased soreness," and "increased comfort"). The duration of relief paralleled the duration for which the protectant remained as a coating over the lesion. Patients with oral hyperkeratosis, geographic tongue and denture stomatitis did not report any subjective improvement.[1]

Although improvement was noted in some patients with idiopathic orolingual paresthesia, it was concluded that the improvement was largely a placebo effect.[1]

Study of Orabase as a Vehicle (Drug-Carrier)

A definitive study[5] of not only the adhesive and protectant properties but also the vehicle properties of Orabase was undertaken. In this investigation triamcinolone acetonide (an active corticosteroid) was incorporated into Orabase as the vehicle and the resultant formulation was topically applied to a variety of oral mucosal lesions.[1]

In many of these patients, the application of the vehicle above (without triamcinolone acetonide) did result in some relief of symptoms but the relief lasted for only that time during which the substance remained in place.[1]

In contrast, triamcinolene acetonide in Orabase was found to exert pronounced suppressant, ameliorative, or curative effects on the various oral mucosal lesions enumerated previously. These effects were much more beneficial than those resulting from the use of Orabase alone, leading to the obvious conclusion that the steroid was being absorbed from the Orabase.

Thus, the decidedly useful action of Orabase as a vehicle was demonstrated. It was also employed as a vehicle for such drugs as dibucaine, tripelennamine, lidocaine, and in tracer studies for the application of sodium fluorescein, and gentian violet. Orabase was also used as a denture adhesive and with considerable advantage.[1]

In vitro Studies

In subsequent in vitro studies of formulations of Orabase with other bases, vehicles, and agents,[4] it was found that all dry compounds or ointments which do not themselves contain water have usually been found to be physically compatible with this adhesive material. Water, however, acts to set the formulation, and hence, contact with water or water-containing ingredients should be avoided.[1]

Orahesive

With continued use of Orabase in the management of wider varieties of oral mucosal lesions, it soon became apparent that Orabase was limited in its efficacy. This was particularly evident in larger sized erosions or ulcerations (larger than 1 - 2 cm in diameter) which could not easily be coated with this vehicle. Furthermore, since Orabase is a paste having considerable bulk and resistance to flow, difficulty was encountered when thin applications were desired. Still another problem encountered was an inability to apply the paste to lesions in the more inaccessible areas of the mouth such as the uvula, the soft palate, the anterior pillars, and the posterior tongue.[6]

In an effort to overcome these problems, studies were undertaken using the same components as in Orabase, except that the mineral oil-polyethylene base was excluded. Thus, a powder vehicle rather than a paste vehicle was

developed and it was applied to the desired oral mucosal site by means of a spray insufflator-dispensing device, a No. 119 De Vilbiss spray atomizer.[6]

Usage of Orahesive as a Vehicle and/or as a Protectant

Orahesive powder, either as an unmedicated protectant or as a vehicle containing active drug ingredients, was administered to a large series of patients, including among these, those with recurrent ulcerative stomatitis, denture stomatitis, lichen planus, idiopathic inflammation and/or ulceration, erosive lichen planus, traumatic ulcer, desquamative gingivitis or stomatitis, idiopathic glossodynia, acute primary herpetic gingivostomatitis, moniliasis geographic tongue, erythema multiforme, radiation stomatitis, chronic discoid lupus erythematosus, pemphigus, oral pyoderma hemophilia, acute leukemia, hyperkeratosis, allergic stomatitis, chemical burn, pericoronitis, vitamin deficiency, antibiotic stomatitis, herpes zoster and socket hemorrhage.[6]

Among the various active agents incorporated in Orahesive and used for treating the above named lesions were: triamcinolone acetonide, mycostatin, amphotericin B, bacitracin, bovine thrombin, chloroquine, lidocaine, methandrostenolone, triamcinolone acetonide monoenenthate, tripelennamine hydrochloride, and vitamin B_{12}.[6]

Just as with the paste vehicle (Orabase), the capacity of the powder vehicle to adhere to the oral mucosae was found to be highly satisfactory. It proved to be far more effective than the paste for reaching the more inaccessible oral lesions, since by properly manipulating the spray dispenser, every site of the oral cavity could be reached. The powder vehicle proved to be advantageous in still another respect, i.e., it could be applied evenly to as large an area as was deemed desirable or indicated. Furthermore,

the thinness of the film which was applied was easily controlled -- of particular importance where the total dosage of active drug incorporated in the vehicle is best kept at minimal levels.[6]

One disadvantage, when compared to Orabase, was that the powder vehicle had, in general, a shorter duration of adherence than the paste formulation. This could be explained on the basis that smaller quantities of the powder were applied per square centimeter of tissue. However, this could easily be overcome by more frequent applications of the medicated formulation.[6]

On the positive side, the therapeutic results obtained through the use of drugs incorporated in the powder paralleled closely the results obtained from the use of the same drugs in equal concentrations prepared in the paste.[3]

In spite of the advantages obtainable through the use of an active agent such as triamcinolone acetonide in Orahesive, therapy with this active agent in Orabase was found to still retain certain desirable and distinctive attributes in the treatment of small lesions in the more accessible regions of the mouth.[7]

Freedom from Untoward Effects

As in the case of Orabase, no evidence of local irritation, local or systemic side reactions, or toxicity was encountered even after repeated applications of the powder-adhesive vehicle, even in a large group of patients who used it as a denture powder over many weeks and months.[6]

Chronic toxicity studies in animals also confirmed its safety both at the site of oral application and systemically.[8,9] Bacteriologic studies revealed no evidence that it stimulated or inhibited the growth of the commonly found oral organisms.[10]

Summary

In summary, the use of the powder formulation was found to be of particular value in the management of oral mucosal lesions of 2 cm or more, and where lesions were located in more inaccessible regions of the mouth.[6]

Crahesive Microporous Tape

Many other individual substances and formulations were included in our long-range studies. Many proved less than useful despite promising beginnings as was the case with Scotch Brand Microporous Surgical Tape (1" width) which unwinds, tears easily, and is microporous in character. The tape was used as the backing for a new intraoral adhesive vehicle-bandage. The surgical tape (a rayon based material) had been in widespread use for application to the skin where it sticks well, is removed easily, is maintained through baths and soak applications, permits drainage and seepage of fluids, and is x-ray transparent. Unfortunately, the tape per se lacks adhesive properties when applied to moist oral mucosal surfaces. Even when a powder adhesive (Orahesive) -- was applied to the tissue surface of the tape prior to its placement over the soft tissue sites of the oral cavity, this formulation too was never found to be clinically useful to any significant degree.[11]

Orahesive Bandage

At about this time efforts were concentrated on developing an intraoral bandage which might serve both as a vehicle and protectant -- a substance which would have the adherence of Orabase or Orahesive and the rigidity of a flexible bandage. A formulation was ultimately discovered consisting of a thin, pliable, easily cut sheet of polyvinyl alcohol on which was layered a thin film of Vistanex (a component of chewing gum) into which

aliquots of Orahesive had been incorporated -- which mixture was dissolved in chloroform (the latter thereafter being evaporated) to permit the "rolling out" process of the mixture on the film as a bandage. A thin adhesive coating of Orahesive powder was then applied to the tissue surface of the polyvinyl alcohol-Vistanex-Orahesive bandage. Initial adhesive-duration times for various oral mucosal tissues appear below:[12]

Tissue site	Number of applications	Duration (in minutes) Range	Average	Median	Mode
Dorsal tongue	31	<5.40	11.3	10	<5
Buccal Mucosa	31	5.30	9.2	10	10
Hard Palate	31	5.55	13.1	10	5

This formulation was prepared in an effort to provide a vehicle base (backing) -- namely, polyvinyl alcohol -- which, after serving its purpose in permitting easy application, would soften and soon dissolve. Thus, whatever active medicinal agent was incorporated into the Orahesive component of the vehicle was easily applied to the desired site and could be administered in an accurately measured quantity. Subsequently, the dissolving backing was replaced by a very thin layer of insoluble Saran (see below).[12]

Initial results suggested that this new formulation did offer certain advantages as a protectant. Although poorly adherent to <u>mobile</u> surfaces, the Saran-backed, greatly improved formulation (by the manufacturers) was later tested by Scopp and others and was found to be highly effective when applied over sockets of teeth or against mucosae backed by bone; etc., as in periodontal care. The vehicle potential of the intravel bandage (where commercially available as Orahesive Bandage) has not been clinically tested.

<u>Long Lasting Lozenges</u>

Throughout the above mentioned investigations much thought and consideration was given to the formulation and utilization of <u>long lasting</u> troches

or lozenges as vehicles for active medications -- lozenges which would assure prolonged and continuous dissolution in the mouth for, preferably, 2 to 4 hour periods. Were such lozenges made available, it was felt that these might indeed become an all-purpose protectant-vehicle for the treatment of many acute and chronic lesions of the mouth. It was also felt that a long lasting lozenge-vehicle might (a) serve as a method for delayed dissolution and absorption of active agents much in the fashion of spansules employed in systemic therapy; and (b) serve as a means of parenteral absorption, by sublingual absorption, thus circumventing the gastrointestinal route in such instances as those in which the active agent is destroyed in the gut.[13]

Standard Lozenges

As an important initial step in these investigations, it was desirable to determine baseline, average dissolution-duration times of various commercially available lozenges and troches. Accordingly, eight brands including candies, cough drops, antibiotic lozenges, etc., were purchased from neighborhood pharmacies and their dissolution-duration times were determined in volunteer dental students using various sites of the mouth. Of a total of 238 test runs, 141 (59%) showed dissolution-duration times of over 10 minutes; 70 (30%) showed dissolution-duration times of over 15 minutes; 46 (19%) showed dissolution-duration times of over 30 minutes; 3(1%) showed dissolution-duration times of over 40 minutes. From these studies it was concluded that the available lozenges or troches were inadequate since their use as vehicles would necessitate repeated administration of lozenges over even a single two to four hour therapeutic period.[13]

Composition of the long Lasting Lozenge

Thus, our specific objective was to formulate a lozenge-vehicle which offered a prolonged dissolution-duration time. After a tremendous amount of work* which necessitated screening nearly a hundred substances for their long lasting dissolution properties, a formulation of methyl cellulose was devised which potentially, at least, appeared promising and was also presumed to be essentially non-toxic. This formulation superceded an earlier far less satisfactory empirical formulation with which we had worked -- the ingredients of which previous lozenge had included carboxymethyl-cellulose, gelatin, pectin and binders.[14]

Various further improvements were made and a formulation coded as CU 701 (prepared by the College of Pharmaceutical Sciences of Columbia University) was extensively tested for its potentially promising dissolution-time properties. The results did prove favorable but the lozenge itself left much to be desired in regard to size, shape, surface roughness, etc. Under the auspices of Forest Laboratories, a new compression technique was devised and perfected which greatly enhanced the necessary and desired physical properties relative to hydration, contour, hardness, and so on. Studies with the latter formulation only are described below.

When this new long lasting lozenge was used as a vehicle it was found that it released minimal but adequate quantities of active medications and thereby facilitated the maintenance of therapeutic concentrations of the drug in the saliva at nearly constant levels throughout the waking hours of therapy.[15]

The active agents which have been incorporated in the vehicle and which are currently under investigation include the following: bacitracin, 2,000

*In collaboration with Dean Joseph L. Kanig of the College of Pharmaceutical Sciences of Columbia University.

units per lozenge; prednisolone, 0.25 mg per lozenge; prednisolone, 5 mg per lozenge; mycostatin, 100,000 units per lozenge; dibucaine, 3 mg; benzocaine, 20 mg; triamcinolone acetonide, 0.25 mg; and triamcinolone, 4 mg.[15]

Other active long lasting lozenge formulations which are being planned will include the following drugs: thrombin, pyribenzamine citrate, vitamin A, methotrexate, Vitamin B_{12}, dimethylsulfixxide, amphotericin B, vancomycin, vitamin C, folic acid, iodine and members of other drug groups, including mucolytics and enzyme digestants.[15]

Use of the Long Lasting Lozenge

There are several potentially useful functions which the long lasting lozenge might fulfill, as noted above.

1) The components of the long lasting lozenge, essentially those which have been described previously, possess adhesive, protectant and demulcent-vehicle properties.

2) The lozenge might serve as a source of systemic therapy wherein gradual and prolonged dissolution takes place in the mouth, whereas absorption takes place in the gastrointestinal tract. In this manner, the long lasting lozenge has properties which parallel those of an ingested delayed-release formulation.[15]

Included in this group of long-lasting lozenge formulations currently under investigation are: prednisolone, 5.0 mg; mycostatin, 100,000 units (gastrointestinal tract effects); and triamcinolone, 4.0 mg.[15]

Other systemically active long-lasting lozenge formulations having this proposed rationale of action are being planned, and include the following: methamphetamine, digoxin, aminophylline, neosynephrine, methotrexate, metariminol bitartrate, potassium chloride, sucrose, meperidine, indocin, sodium bicarbonate, pyribenzamine citrate, and vitamin A.[15]

3) Still another function which long-lasting lozenges might perform is that of releasing medications (i.e., insulin, heparin) which are absorbed through the oral mucosae, but which might be destroyed or inactivated in the gastrointestinal tract. Similarly, for vitamin B_{12}, in patients with pernicious anemia.[15]

Included in the long-lasting lozenge formulations under investigation in this category are for formulations of epinephrine: 1.0 mg and 0.5 mg per lozenge for the management of bronchial asthma.[15]

Clinical Studies: Dissolution Time of Long Lasting Lozenge

Clinical studies utilizing student volunteers revealed that the minimal duration time for the dissolution of a long lasting troche was fifty minutes and the maximum was over four hours and forty minutes. The average time was calculated at approximately two hours and a half.[14]

In 36 clinic patients, the average duration time for complete dissolution or fragmentation of troches was three hours and four minutes, with a maximum time of twelve hours (one instance), and a minimum time of thirty minutes (one instance).[14]

The results of more extensive clinical trials (572) with these lozenges in 13 male dental students are summarized as follows: the range of dissolution for all lozenges in all subjects was 20 minutes to 520 minutes (8 hours, 40 minutes); the mean for all lozenges in all subjects was 145 minutes (2 hours, 15 minutes); the mode for all lozenges in all subjects was 135 minutes (2 hours, 15 minutes); the mean of individual subject means for all lozenges and subjects was 155 minutes (2 hours, 35 minutes); and the mean of individual subject medians for all lozenges and subjects was 150 minutes (2 hours, 30 minutes).[16]

A similar study was performed with nine female dental hygiene students. The results of their 820 clinical trials are summarized as follows: the range of dissolution for all lozenges in all subjects was 16 minutes to 153

minutes (2 hours, 33 minutes); the mean for all lozenges in all subjects was 68 minutes (1 hour, 8 minutes); the median for all lozenges in all subjects was 66 minutes (1 hour, 6 minutes); the mode for all lozenges in all subjects was 45 minutes; the mean of individual subject means for all lozenges and subjects was 70 minutes (1 hour, 10 minutes); and the mean of individual subject medians for all lozenges and subjects was 69 minutes (1 hour, 9 minutes).[16]

Clinical examinations and questioning of subjects revealed no objective evidences of tissue irritation and no subjective complaints. The troche generally caused an initial sensation of local dryness followed by a moist, slippery feeling; the troche was generally considered innocuous and although not entirely pleasant because of its sticky qualities there were no complaints that it was disagreeable. No gastrointestinal disturbances were experienced by any subjects.[16]

Therapeutic Efficacy of the Long-Lasting Lozenge

A number of the above-mentioned formulations have already been studied in considerable detail and favorable clinical impressions have been obtained.

One study included a total of 46 patients with erosive lichen planus, with lichen planus, recurrent ulcerative stomatitis, recurrent ulcerative scarifying stomatitis, desquamative gingivitis, erythema multiforme, pemphigus, chronic discoid lupus erythematosus, idiopathic glossodynia, chronic benign pemphigoid, an undiagnosed, fixed ulcerative condition, and one patient with hyperkeratosis. In the treatment of all patients listed above, triamcinolone acetonide, incorporated in the long-lasting lozenge in a dosage of 0.25 mg, was used as the active medication. Most patients were instructed to take three (and if possible, four) lozenges daily, preferably one after each meal and one before retiring. Thus, a maximum of 1.0 mg of triamcinolone acetonide was administered to the lesion(s) during the course of each treatment

day. As a matter of fact, it was almost impossible to consume more than four long-lasting lozenges (or 8 -- if 2 lozenges were introduced as a "dose" rather than one) per day, since the prolonged dissolution time of the lozenges practically precluded this. In many instances, the dosages of the active agent administered each day were considerably less than 1.0 mg, when instructions to employ a lower dosage were given or when the patient was unable to use more than two or three long-lasting lozenges per day.[17]

The results of therapy with 0.25 mg triamcinolone acetonide long-lasting lozenges in treating these oral mucosal lesions are tabulated below:[17]

	No. of Cases	No Change	Degree of Improvement (No. of Cases) 10%	25%	50%	75%	90%	100%
Desquamative Gingivitis	5	0	0	2	3	0	0	0
Recurrent Ulcerative Stomatitis	5	2	0	0	0	1	2	0
Recurrent Ulcerative Scarifying Stomatitis	2	0	1	0	0	1	0	0
Erythema Multiforme	6	0	0	1	5	0	0	0
Pemphigus	2	1	0	0	1	0	0	0
Chronic Discoid Lupus Erythematosus	1	0	0	0	0	1	0	0
Idiopathic Glossodynia	3	1	0	1	1	0	0	0
Chronic Benign Pemphigoid	1	0	1	0	0	0	0	0
Hyperkeratosis	1	0	0	0	1	0	0	0
Erosive Lichen Planus	14	1	0	4	6	1	2	0
Lichen Planus	5	1	0	1	3	0	0	0
Undiagnosed Fixed Ulcerative Stomatitis	1	0	1	0	0	0	0	0
Total	46							

Using one such disease as an example, lichen planus, of the 14 corticosteroid treated cases: none was found to be 100 per cent improved; one case showed no improvement; four cases were found to be minimally improved; six cases moderately improved; one case markedly improved; while two cases were found to be approaching full healing. The average improvement score was found to be of the order of just over 50 per cent. Since the therapeutic agent chosen for incorporation in the long-lasting lozenge in this study for treating the

above listed diseases was a corticosteroid, and, since it was expected that the steroid would at most exert an anti-inflammatory-suppressant action, curative results were not anticipated. And, as the above table illustrates, no "cures" were obtained. However, the suppressant action of the corticosteroid incorporated in the long-lasting lozenge was well demonstrated in many cases by the considerable improvements reported.[17]

By contrast, of the 11 placebo-treated cases, 3 cases were moderately improved, 2 minimally improved and six cases showed no change.[17]

Side Effects

It is important to emphasize that no undesirable side effects could be attributed to the triamcinolone acetonide, long-lasting lozenge therapy, nor were there any undesirable side effects observed in any of the placebo long-lasting lozenge treated patients.[17]

Studies of Efficacy of Drug Release

In another clinical study 11 dental hygiene students of Columbia University, all females, age 19 to 24 years, served as subjects for determining the topical anesthetic effectiveness of a local anesthetic (20 mg benzocaine) incorporated in a 12-grain long-lasting lozenge. Each subject was given 5 randomly coded pairs of identically appearing lozenges, one of each pair containing 20 mg of benzocaine, the other being a placebo to assure a double blind approach. Each subject was instructed to self-administer one pair of lozenges per day, taking one in the morning and the other in the evening with a minimum of three hours intervening. Each subject was asked to record the dissolution time of each lozenge and to subjectively evaluate the anesthetic action of the lozenge, if any. Where anesthesia was determined as being present, it was to be graded as follows: 1+ = slight anesthesia; 2+ = moderate anesthesia; and 3+ = intense anesthesia.[18]

Of the 54 paired trials, 51 resulted in positive anesthesia with the benzocaine-containing lozenges. It is interesting to note that in the 55th trial the subject was erroneously given a pair of lozenges which were both placebos and that the subject reported anesthesia from one of the placebos! Of the 51 positive anesthetic results, 44 were considered 1+; 7 were considered 2+; there were none which were deemed to be intense (3+) anesthesia. Of the 56 placebo trials, 52 were rated as 0 and 4 were considered 1+ anesthesia. There were no instances of 2+ or 3+ anesthesia. In most instances of anesthesia, the subject reported that the onset occurred within 15 minutes of the insertion of the lozenge and that the anesthesia lasted for about 15 minutes after its complete dissolution. The dissolution time for all lozenges in this study ranged from 30 to 224 minutes with a mean of 100 minutes and a median of 105-106 minutes.[18]

Additional Uses Hypothesized for the Long-Lasting Lozenge

Although several of the potentially useful properties of a long-lasting lozenge have been realized or are under study, there are many other possible uses which suggest themselves and also demand extensive investigation -- to mention but a few: 1) for the treatment of certain inflammatory and ulcerative diseases of the pharynx, larynx, and esophagus through the use of long-lasting lozenges containing antibiotics, topical corticosteroids, topical antiseptics, topical anesthetics, etc. 2) for the slow release of anticaries, calculus-inhibiting, and dentine desensitizing agents when incorporated in long-lasting lozenges. 3) for slow and prolonged release of antacids from long-lasting lozenges into the gastrointestinal tract which regimen might exert a more beneficial action than is obtained when these same agents are rapidly ingested in the usual manner (in fact, the unmedi-

cated long-lasting lozenges, which contain principally methylcellulose, may well prove per se to be an effective antacid formulation). 4) for the incorporation of artificial sweeteners included in placebo lozenges or of specifically active agents -- appetite suppressants. 5) the availability of unsweetened lozenges, with or without medications, for use by diabetics and so forth.[15]

UNDERGRADUATE DENTAL STUDENTS WHO RECEIVED SUPPORT (PARTIAL) FROM CONTRACT FUNDS AND WHO SUBSEQUENTLY RECEIVED D.D.S. DEGREE

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Martin S. Greenberg

Richard Lo (Master of Science)

Ronald Montana

William Montano

David Schwartz

Thomas Tong

Howard Weintraub

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